

The claims of the application have been amended in a manner to overcome certain objections raised by the Examiner in the recent Official Action and in a sincere effort to place the application in immediate condition for allowance.

Thus, claims 20 and 21 are cancelled without prejudice to the subject matter involved. While Applicants do not concur in the position advanced by the Examiner that these claims are subject to rejection under the provisions of 35 U.S.C. 112, these claims are cancelled in an effort to reduce the issues outstanding in the application.

Furthermore, a minor clerical correction is effected in claim 25.

Claims 20 to 23 are rejected as failing to adequately define the invention under the provisions of 35 U.S.C. 112. The Examiner urges that the disclosure is enabling only for claims limited to the specified ratios of artemether to benflumetol. Applicants respectfully traverse the position of the Examiner in this regard. Insofar as claims 22 and 23 are concerned, particular attention is directed to page 7 of the specification, the first full paragraph. At this point in the specification, the compositions of claims 22 and 23 are fully disclosed. Furthermore, in the specification, the Applicants have clearly taught the art-skilled how to prepare and how to use these compositions. Thus, the position taken by the Examiner to the effect that the disclosure is not enabling for the full scope of these claims is completely untenable and should be reconsidered and withdrawn.

In a sentence set forth by the Examiner spanning pages 3 and 4 of the Official Action, the Examiner has raised an issue which the Applicants believe must be discussed at this point. Thus, the Examiner states:

"Finally, with regard to synergism, any claims broader in scope than the original specification, even if shown by the declaration, would not be allowed due to the introduction of new matter."

In respect to this point, Applicants respectfully submit that no claims are presented which are broader than the specification. The specification of the present application clearly discloses compositions containing a mixture of the individual components claimed herein which are synergistic in the treatment of malaria. The specification clearly enables one skilled in the art to formulate such compositions and to use them in the treatment of malaria. Applicants thus respectfully submit that it cannot properly be said that any of the claims of the present application are broader in scope than the original disclosure. The Examiner is respectfully requested to reconsider and withdraw any position to the contrary.

The claims are rejected as lacking patentability under the provisions of 35 U.S.C. 103 over Wang et al. and Sethi et al.. This ground of rejection is deemed to be untenable and is thus respectfully traversed.

In making this ground of rejection, the Examiner urges that the compositions and method for treatment of malaria as claimed are *prima facie* obvious to one of ordinary skill in the art based upon the teachings, in the references, of the prior employment of the individual components for the same purpose.

Applicants have previously pointed out that they question, as a general proposition, whether it can be properly said that merely because each of the individual components is known in the treatment of malaria, it would be *prima facie* obvious to the art-skilled to employ a combination of these materials in the treatment of malaria. Be that as it may, however, the Examiner does appear to appreciate the basic proposition that if true synergistic action in the combination as established, any presumption of *prima facie* obviousness will be overcome.

With their response of August 27, 1992, Applicants have submitted the Declaration of Dr. Walther H. Wernsdorfer. Applicants respectfully submit that the Declaration of Dr. Wernsdorfer does in fact clearly establish the requisite synergism to exist and thus is sufficient to overcome any presumption of obviousness which may be said to be raised by the teachings of the references.

In the most recent Official Action, the Examiner has indicated that the Wernsdorfer Declaration has been considered but is deemed to be unpersuasive. In this respect, the Examiner states:

"The expected values in tables 1 and 2 are confusing and unclear. The values do not reflect the 'expected' additive effect from combining the observed values for each compound alone. It is not clear as to why the 'expected' value are lower than what would be normal for an additive effect."

This criticism on the part of the Examiner has been discussed with Professor Wernsdorfer and he confirms the correctness of all values in Tables 1 and 2 including the "expected" ones.

Prof. Wernsdorfer raises the point that to the Examiner the expected values appear higher if taken from the *arithmetical* mean of the individual values (popularly defined as average), see Table 1, EC_{50} of the 1:1 mixture. Based on 0.5730 for A alone and 2.0948 for B alone the expected value for the 1:1 combination would appear: 1.3339 [0.5730 (observed for A alone) + 2.0948 (observed for B alone) divided by $2 = 1.339$]. The criticism is based on the fact that the lower value of 1.0956 has been defined as expected instead of 1.339 .

Prof. Wernsdorfer insists that the expected value should be calculated from the *geometrical* rather than the arithmetical mean of the individual values. The geometrical mean generally results in an average *lower* than the arithmetical mean. Calculating the geometrical mean is intended to reduce the influence of individual deviations on the average. A geometrical mean represents the average based on individual experimental values better than the arithmetical mean. In the instant case, a series of expected values for the 1:1 mixture and for the 1:2 and the other mixtures respectively, is calculated from the observed individual values for A and B alone. Calculating the geometrical mean of those individual expected values results in the expected values of 1.0956 , 1.3598 and others criticized as being too low by the Examiner.

What Prof. Wernsdorfer intends to say is illustrated by the following: 0.5730 (A alone) taken to the square power is 0.3283 . 2.0948 (B alone) also taken to the square power is 4.3881 . The product of both: $0.3283 \cdot 4.3881 = 1.441$. The square root of this product represents the geometrical mean: $\sqrt{1.441} = \underline{1.200}$.

This clearly illustrates the fact that the geometrical mean of 1.200 is lower than the arithmetical mean of 1.3339 expected by the Examiner. The fact that 1.0956 has been calculated as expected value instead of 1.200 is simply explained by the fact 0.5730 and 2.0948 and, correspondingly, the other values for A and B alone, already represent geometrical means values. Referring to the above, it is not quite correct to calculate the geometrical mean of the 1:1 mixture from geometrical means of A and B alone. The expected values for the mixtures are calculated in reality as geometrical means from individual expected values and this results in the values shown in the Declaration being even lower than 1.200. The value of 1.200, therefore, only represents an approximation. But, this approximation makes clear that the expected value calculated from a geometrical mean is lower than the expected value calculated from an arithmetical mean.

Thus, Applicants respectfully submit that the criticism of the Examiner in this regard is simply not correct. The Examiner is respectfully requested to reconsider the Wernsdorfer Declaration in light of the comments set forth above.

Next, the Examiner urges that the Declaration is not convincing in view of the fact that the claims are not limited to the organisms tested. This objection is likewise deemed to be untenable.

Initially, Applicants would point out that this objection has no relevance to the compositions themselves. Secondly, with regard to the method of use claim 25, Applicants respectfully submit that the organism tested is clearly illustrative of the malarial causing microorganisms and Applicants are not aware of any reason why the art-skilled would expect that the

would be significantly different with other malarial causing microorganism strains. Certainly the Examiner has not set forth any scientific reasoning to so believe.

Finally, the Examiner urges that the claims are not limited to the compounds tested. That criticism is likewise deemed to be untenable and is respectfully traversed.

Initially, it is pointed out that in the combination of components, the first component comprises only the single compound benflumetol. The activity of this single compound in the claimed composition has certainly been shown in the Declaration.

It is true that the second component of formula (II) comprises a small group of compounds. All of the compounds within the scope of formula (II) are, however, structurally analogous, are of the same natural origin (artemisia plant) and are all known as effective anti-malarial agents. One skilled in the art may reasonably expect the results for one of the compounds within the scope of formula (II) to be similar or analogous to those established with the artemether derivative according to the Wernsdorfer Declaration. Here also, Applicants are not aware of any reason why one skilled in the art would not expect similar results to be achieved and thus respectfully submit that the artemether derivative is illustrative of this group of compounds. Surely the Examiner has not pointed out any scientific basis upon which to urge that one skilled in the art would expect significant differences in the results to exist.

Based upon the foregoing, Applicants respectfully submit that the Examiner's criticisms of the Declaration of Dr. Wernsdorfer are simply not valid criticisms and that such criticism should be reconsidered and withdrawn.

Based upon the foregoing, Applicants respectfully submit that each of the grounds of rejection set forth against the present application has been overcome and that the application is now in condition for allowance; such allowance is solicited.

Respectfully submitted,

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